

Use of Intravenous Immunoglobulins for Prophylaxis or Treatment of Infectious Diseases

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By the advent of the era of antimicrobial drugs, passive immunization with pathogen-specific animal (usually horse, cow, or rabbit) sera for the prophylaxis or treatment of certain bacterial infections, bacterial toxin-mediated diseases such as tetanus, or serious viral infections such as rabies had become very sophisticated (13, 39, 43). Antimicrobial chemotherapy made it no longer necessary to expose patients to the serious risks posed by injection of animal sera for the treatment of pneumonia and sepsis. It is paradoxical that 60 years later, antimicrobial resistance of some bacterial and viral pathogens, new iatrogenic diseases arising from aggressive therapies for cancer or organ failure, and improved understanding of the pathogenesis and immunology of viral and bacterial infections have brought renewed interest in passive immunization for the prevention and treatment of certain infectious diseases.

Nearly 50 years have passed since Ogden C. Bruton's report of an 8-year-old boy with recurrent *Streptococcus pneumoniae* bacteremia whose plasma contained little gamma globulin (immunoglobulin G [IgG]). Bruton treated the boy's agammaglobulinemia with regular intramuscular (i.m.) injections of human-plasma-derived IgG. The treatment resulted in increased serum IgG levels and an impressive reduction in the number of serious bacterial infections he experienced (6). At the time of Bruton's report, few appreciated the implications of his seminal observations.

Near the end of World War II, Edwin Cohn's pooled human plasma "fraction 2" was injected intramuscularly to control outbreaks of red measles and infectious hepatitis in U.S. soldiers (7, 34, 53). Soon after, fractionated IgG became generally available for i.m. use. At that time, human IgG treatment was recommended to modify disease expression of measles and hepatitis A, but other indications for its clinical use were not fully defined. As IgG could be safely given only by the i.m. route, doses were limited to about 100 to 150 mg/kg of body weight/month. Larger doses were too painful. In the decades following Bruton's report, the development of simple and reliable IgG assays permitted the identification of additional hypogammaglobulinemic patients. Also identified were preterm neonates, some other normal infants with transient low IgG levels in the first year of life, older infants, and occasional children and adults with congenital or acquired hypogammaglobulinemia (51). In the past 25 years, patients with lymphoid malignancies or those who were immune suppressed for organ transplantation or undergoing therapy for cancer were found to commonly experience serious infections. Might these pa-

tients also benefit from immune augmentation with IgG? When empiric parenteral immunoglobulins were given to these patients, it remained uncertain whether they experienced significantly fewer serious infections.

An assumption underlying IgG formulations was that plasma pooled from large numbers of donors ensured that IgG lots contained comparable levels of antigen-specific antibodies. Despite this assumption, we and others demonstrated substantial lot-to-lot differences in neutralizing (NT) antibody levels for respiratory syncytial virus (RSV) and for specific opsonic antibodies to group B streptococci (GBS) (16, 18). Manufacturers were not required to quantify specific antibody content in their preparations. Hence, practitioners could not be confident of the quantities of pathogen-specific antibodies present in any given production lot of IgG.

To overcome the dosing limitations of injectable IgG, techniques were developed to prepare IgG for safe intravenous (i.v.) administration. By the early 1980s, several IgG preparations were licensed for i.v. use (IVIg), permitting as much as 10- to 20-fold increases in the amounts that could be given. (Table 1). The new technology also permitted the preparation of human hyperimmune globulins recommended for the prevention or treatment of tetanus, botulism, hepatitis B, rabies, and varicella (Table 2) (2).

Today, with more than 50 years of clinical experience with generic pooled human IgG for general treatment and/or prevention of infectious diseases, the only clear indications for use, with the exception of specific recommendations for the prevention of hepatitis A and measles, are congenital or acquired deficiencies in immunoglobulin production. Whether IgG or IVIg benefit patients with iatrogenic immunodeficiencies remains less certain.

A new era in infectious disease prevention began with the June 1998 Food and Drug Administration (FDA) licensing of palivizumab (Synagis) (9). Palivizumab is a "humanized" mouse monoclonal antibody formulated to prevent RSV pulmonary infections in high-risk patients, especially infants and young children. Human and humanized monoclonal antibodies seek to overcome several shortcomings of IVIg preparations by targeting specific viral or bacterial antigens responsible for disease pathogenesis. They improve safety by substantially reducing the amounts and diversity of proteins that must be given. As monoclonal antibodies are not derived from human blood, the risk for contamination with hepatitis B or C virus, HIV, or other blood-borne viruses is markedly reduced.

This brief review will summarize contemporary indications for IVIg infectious diseases prophylaxis and examine recommendations for use of the recently engineered monoclonal antibody palivizumab for prevention of RSV infection (19, 36).

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TABLE 1. Licensed IgG products available in the United States^a

Product	Composition ^b
Baygam	Generic
Bayhep B.....	High-titer hepatitis B
Bayrab.....	High-titer rabies
Baytet.....	High-titer tetanus
Cytogam.....	High-titer CMV
Gamimune N, 5%	Generic
Gammagard S/D.....	Generic
Gammar-P i.v.....	Generic
Iveegam EN IGIV.....	Generic
MICRhoGAM	Hyperimmune
Sandoglobulin	Generic

^a From reference 37.^b Polyclonal, human-plasma derived.

CLINICAL UTILITY OF IVIg

Premature infants. In 1955, Orlandini et al. (35) documented that maternally derived IgG levels in term infants' cord blood serum usually exceeded maternal levels. Rapid growth of the infant and protein catabolism cause IgG levels to drop rapidly after birth, to levels sometimes less than a quarter of birth levels by 4 to 6 months of age. Preterm infants have less IgG at birth and experience the moderately severe hypogammaglobulinemia of early infancy. i.m. treatment of infants with IgG, as reported by Steen (49) and Amer et al. (1), appeared not to reduce the incidence of serious infections. Though IgG-IVIg prophylaxis-treatment is recommended for infants whose mothers have hepatitis A, measles, or poliomyelitis infections

TABLE 2. Passive immunization^a

Clinical indication	Immunization
Hepatitis A.....	Immunoglobulin may be administered prophylactically (i.m.) at a dose of 0.02 ml/kg if exposure is in ≤ 2 wk
Hepatitis B.....	Hepatitis B immunoglobulin given in 2 doses; the first as soon as possible and the second, 0.06 ml/kg (i.m.), in a mo
Measles.....	Immunoglobulin given within 6 days of exposure, 0.25 ml/kg (i.m.) or IVIg, 100–400 mg/kg (higher doses for severely immunocompromised patients)
Varicella	Varicella immunoglobulin from Red Cross Blood Services for i.m. administration (each vial contains 1.25 ml containing about 125 U; suggested maximal dose, 625 U); must be given within 96 h of exposure
Rabies.....	Rabies immunoglobulin (from hyperimmunized human donors) given i.m. at 20 IU, with as much as possible infiltrated around the wound and the remainder i.m. with a new needle
Tetanus.....	Human tetanus immunoglobulin in a single dose of 3,000–6,000 U i.m.—some recommend injection of a portion around the site of infection; if not available, IVIg is recommended, though dosage is not known
RSV	Respigam at 750 mg/kg i.v. monthly for certain infants with chronic lung disease during RSV season
CMV	Cytogam at 150 mg/kg for seronegative transplant patients followed by gradually decreased doses every 2 wk for 16 wk

^a From reference 2.

at or near the time of parturition, most other possible indications for infectious disease prophylaxis remain speculative (50). IVIg treatment appeared to improve the outcome of an echovirus 11 infection in a patient with agammaglobulinemia (28), as well as in a nursery outbreak of echovirus 11 (32). These and other studies implied that prophylaxis or treatment with IgG might be beneficial if sufficient levels of agent-specific antibodies were present. About 20 years ago, in vitro (21) and in vivo (16) modeling showed that for treatment of GBS infections IgG must contain sufficient quantities of specific functional antibodies to affect bacterial killing and clearance. These and complementary data led to prospective treatment trials with IVIg or with GBS hyperimmune IVIg to reduce mortality rates in infants at risk for perinatal GBS infection. These large and complicated studies yielded equivocal results (54, 55). Coincidentally, other neonatal sepsis prevention trials were conducted. The National Institutes of Health-sponsored Neonatal Research Network conducted prophylactic studies with a large group of very-low-birth-weight infants. IVIg failed to reduce the incidence of hospital-acquired infections in these infants (15). Baker and associates conducted a similar large trial with similar results (5).

Despite the discouraging results, interest in the use of IVIg for prevention of neonatal infections continued. A November 2000 report by Sandberg and associates (42) compared infection prophylaxis results for preterm infants with cord blood IgG levels of ≤ 4 g/liter with the results for those with higher levels. Babies received 1 g of IVIg per kg on days 0, 3, 7, 14, and 21 ($n = 40$) or placebo ($n = 41$). Again, no significant reduction in infectious episodes or mortality was observed in the IVIg-treated subjects compared to placebo recipients. H. R. Hill, in an editorial response to the Sandberg study noted that based on “the study by Sandberg et al., and the other controlled studies in the literature, IVIg should not be used in an attempt to prevent nosocomial infections in premature infants” (23).

Ohlsson and Lacy conducted a recent meta-analysis (33). Data were combined from multiple randomized, placebo-controlled studies of immunoglobulin for the prevention of nosocomial infections in preterm or low-birth-weight infants. Among the 5,054 infants included in the analysis, only a slight reduction in sepsis (3 to 4%) and no changes in other morbidities were found.

Clearly, perinatal, later-onset, and nursery-acquired bacteremia, pneumonia, soft tissue infection, and sepsis are far more complicated in their pathogenesis than just reduced levels of IgG. The multiplicity of studies conducted during the past 20 years confirm that IVIg treatment is only marginally useful in the prevention or treatment of these serious neonatal infections. The treatment is expensive and presents an additional risk of exposing recipients to blood-borne pathogens. Hence, the prophylactic use of IVIg for the prevention of neonatal nosocomial infections should be discouraged. There remains hope that monoclonal antibody preparations, selected for specific antigenic targets, may yet make it possible to reduce the incidence of GBS, gram-negative enteric-pathogen, and staphylococcal infections. However, any new prophylactic monoclonal antibody preparation will require rigorous testing in blinded, placebo-controlled trials.

Bacterial sepsis syndromes in adults. IVIg prophylaxis and treatment of bacterial sepsis syndromes in adults have also yielded equivocal results. Alan Cross wrote in 1995, "this form of adjunctive therapy has been implemented for infectious but also for noninfectious conditions, often in the absence of convincing data to establish its efficacy" (10). Werden's recent report supports Cross's analysis (56). Yet recently, Douzinas and colleagues reported that high-dose IVIg (250 mg/kg/day infused on days 2, 3, and 6) significantly reduced the incidence of septic complications in a small group of patients hospitalized following serious trauma (12). Larger studies are required to confirm these observations. Despite such occasional reports to the contrary, neither IVIg prophylaxis nor treatment is clearly beneficial for prevention of nosocomial bacterial infections in ill or immunocompromised adults. Whether pathogen-specific monoclonal antibodies or well-defined hyperimmune immunoglobulins will ultimately benefit sepsis-prone adults remains to be determined.

Antibody prophylaxis and treatment of RSV infections. (i) Animal studies. Studies conducted with cotton rats in the 1980s demonstrated that parenteral administration of human IVIg containing large quantities of RSV NT antibodies significantly reduced in vivo RSV replication in nasal mucosa and lungs. From these observations it was hypothesized that infusion of sufficient amounts of RSV antibodies might be useful for treatment and for prophylaxis of RSV infections in infants and young children (20, 36, 38).

(ii) Human studies. Despite animal evidence suggesting therapeutic efficacy, in well-conducted clinical trials in which NT levels were known IVIg treatment did not significantly shorten the duration of hospitalization of infants with RSV bronchiolitis and/or pneumonia (22, 40, 41).

Prophylaxis with high-titered human polyclonal RSV IVIg (Respigam) does not significantly reduce the incidence of RSV infections. However, monthly prophylaxis significantly reduced the severity of RSV infections in very young high-risk patients who became infected with RSV (9, 17). Reductions in hospitalization rates and significantly shorter hospital stays compared to well-matched control patients were observed (9, 17). Yet, Respigam is expensive and requires insertion of a venous line for i.v. administration. Infusions of 750 mg of RSV IVIg per kg are necessary at least monthly to provide sufficient protection. Production challenges, the task of finding populations of high-NT plasma donors, the cost, and the difficulty in the administration of RSV IVIg prompted the development of a humanized mouse monoclonal antibody (palivizumab) directed against a critical neutralizing epitope located on the RSV fusion protein. As with Respigam, in the 1996–1997 (Impact) clinical trial palivizumab, 15 mg/kg administered i.m. once each month, did not reduce RSV infection rates. Rather, it resulted in significant reductions in RSV infection severity, manifested as reduction in hospitalization rate ($P = 0.00004$) and duration of hospitalization ($P < 0.001$) for high-risk infants (24). Palivizumab was licensed by the FDA in June 1998 for RSV infection prophylaxis for certain preterm infants and neonatal intensive care nursery graduates with chronic lung disease.

A retrospective follow-up analysis of palivizumab recipients from nine sites across the United States compared the results from the first year of licensed clinical use with infants enrolled

in the Impact trial (24). Data were reviewed for 1,839 children, each of whom had received at least one palivizumab injection, between September 1998 and May 1999. The investigators found a 2.9% RSV-related hospitalization rate for palivizumab recipients compared to a 4.8% rate for patients enrolled in the Impact trial. However, since there was not a control group for this study, the results cannot be fully compared (47). Based on existing trial data and FDA approval, the American Academy of Pediatrics' Committee on Infectious Diseases recommends palivizumab for RSV prophylaxis for "infants and children younger than two years of age with chronic lung disease (CLD) who have required medical therapy for CLD within six months before the anticipated RSV season" (3). Clinical trials are under way examining whether palivizumab may benefit transplant and cancer patients who are also at high risk for serious RSV infections.

IVIg and CMV infections in transplant patients. Cytomegalovirus (CMV) infection emerged as a serious problem for patients immunocompromised by treatment for malignancies or organ transplantation. In 1983–1984 Meyers and coworkers (29) and Condie and O'Reilly (8) reported that serious CMV infections may be attenuated or prevented by passive immunization with "cytomegalovirus immune globulin." Cytomegalovirus immunoglobulin (CIg) was licensed in 1991 and has regularly been utilized to reduce CMV morbidity and mortality. Treatment is expensive and does not always prevent serious CMV disease in severely immunocompromised patients. For these patients, it is imperative that other preventive strategies also be employed. These include serologic matching of patients and donors, screening of blood and plasma for CMV antibodies to confirm prior infection, and where possible, reducing transplantation of organs from CMV-positive donors to CMV-negative recipients. Several studies demonstrate that CIg infusion moderately reduces serious CMV infections associated with renal and liver transplants and improves survival of infected patients (14, 44, 45, 46). Efforts to further reduce infection rates or improve survival of CMV-infected patients by adding prophylactic ganciclovir only slightly improved clinical outcomes (25). In summary, CIg prophylaxis is indicated for patients at risk for CMV infections following solid organ and perhaps bone marrow transplantation. For patients receiving organs from CMV-positive donors, prophylaxis may be improved by concomitant ganciclovir therapy.

IVIg or hyperimmune IVIg in prevention and treatment of mother-infant HIV infection. (i) Transmission. Infants and children with AIDS benefit from IVIg therapy together with antiviral therapy if they are also hypogammaglobulinemic (IgG < 250 mg/dl) or have had two or more serious bacterial infections in the previous year. Other indications for passive immunization with IVIg include parvovirus B19 infection, failure to make specific antibodies after immunization, immune-mediated thrombocytopenia, and adjunctive therapy for HIV-infected children with bronchiectasis (2, 30, 48).

A hyperimmune IVIg preparation has also been prepared (11, 26). hyperimmune IVIg administered with zidovudine appeared to reduce mother-infant transmission compared to a control group receiving zidovudine and IVIg (52). The low HIV transmission rates in both arms of this study confirmed that zidovudine prophylaxis is highly effective, even for women with advanced HIV disease, but could not address whether

passive immunization diminishes perinatal transmission of HIV. Much remains to be learned about the role of NT antibody in HIV infection. Recent studies with macaques (4, 27) showed that passive immunization and maintenance of high titers of NT antibodies protect mucosal surfaces from infection when they are challenged with substantial doses of HIV (31). The relevance of these observations to the prevention of HIV infection in humans remains to be studied.

SUMMARY

Prophylactic polyclonal human IVIg is indicated for infectious disease prophylaxis for patients of all ages with primary or secondary agammaglobulinemia. Such treatment has markedly reduced infectious morbidity and mortality for these patients. The use of IVIg in immunocompromised patients, such as preterm infants, or those undergoing cancer chemotherapy, bone marrow transplantation, or transplantation of solid organs, has not significantly reduced the incidence of bacterial sepsis syndromes in these patients. Their general use should be discouraged.

IVIg and pathogen-specific hyperimmune IVIg prophylaxis are indicated to modify or prevent certain viral syndromes including hepatitis A, hepatitis B, measles, varicella, and rabies. Specific immunoglobulins may be indicated for prevention of tetanus and botulism for patients at risk. They also appear to be useful in treatment of enteroviral central nervous system infections in patients with agammaglobulinemia and in reducing infectious morbidities during enteroviral nursery epidemics. CIg appears to reduce CMV disease severity for some severely immunocompromised transplant patients. Whether Respigam or palivizumab is efficacious in preventing or reducing the morbidity of RSV pneumonias in transplant patients remains to be determined. The evidence is compelling that palivizumab prophylaxis reduces RSV disease severity in preterm infants and neonatal intensive care graduates with chronic lung disease. A season's treatment is expensive and debate continues over whether general use is cost-effective. Still, for some patients, the prevention of hospitalization justifies the great expense.

IgG or IVIg efficacy for preventing or modulating bacterial toxin-mediated diseases such as tetanus, botulism, and diphtheria is undisputed. Less clear is whether they might be used in mediating the physiological consequences of certain streptococcal or staphylococcal infections. It is evident, however, that preparations must contain the requisite kinds and amounts of antigen-specific antibodies to be effective.

The success of palivizumab and other monoclonal antibody preparations will encourage the development of monoclonal antibodies that may prevent other serious bacterial and viral infections that afflict high-risk patients. One can imagine the development of such antibodies for the prevention of nosocomial staphylococcal and antibiotic-resistant-enterococcus infections. Monoclonal antibodies should also be developed and studied for acute prophylaxis of influenza and parainfluenza virus infections for high-risk patients, such as infants, transplant patients, the elderly, persons with cystic fibrosis or other chronic pulmonary diseases, and perhaps some patients with AIDS.

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REFERENCES

- Amer, J., E. Ott, F. A. Ibbott, D. O'Brien, and C. H. Kempe. 1963. The effect of monthly gamma-globulin administration on morbidity and mortality from infection in premature infants during the first year of life. *Pediatrics* **32**:4-9.
- American Academy of Pediatrics. 2000. 2000 Red Book: report of the Committee on Infectious Diseases, 25th ed., p. 42-44. American Academy of Pediatrics, Elk Grove Village, Ill.
- American Academy of Pediatrics. 2000. 2000 Red Book: report of the Committee on Infectious Diseases, 25th ed. American Academy of Pediatrics, Elk Grove Village, Ill.
- Baba, T. W., V. Liska, R. Hofmann-Lehmann, J. Vlasak, W. Xu, S. Oyejunie, L. A. Cavancini, M. R. Posner, H. Katinger, G. Stiegler, B. J. Bernacki, T. A. Rizvi, R. Schmidt, L. R. Hill, M. E. Keeling, Y. Lu, J. E. Wright, T. C. Chou, and R. M. Ruprecht. 2000. Human neutralizing monoclonal antibodies of the IgG1 subtype protect against mucosal simian-human immunodeficiency virus infection. *Nat. Med.* **6**:200-206.
- Baker, C. J., M. E. Melish, R. T. Hall, D. T. Casto, U. Vasan, L. B. Givner, and the Multicenter Group for the Study of Immune Globulin in Neonates. 1992. Intravenous immune globulin for the prevention of nosocomial infection in low-birth-weight neonates. *N. Engl. J. Med.* **327**:213-219.
- Bruton, O. C. 1952. Agammaglobulinemia. *Pediatrics* **9**:722-728.
- Cohn, E. J., J. L. Oncley, L. E. Strong, W. L. Hughes, Jr., and S. H. Armstrong, Jr. 1944. Chemical, clinical, and immunological studies on the products of human plasma fractionation. I. The characterization of the protein fractions of human plasma. *J. Clin. Investig.* **23**:417-432.
- Condie, R. M., and R. J. O'Reilly. 1984. Prevention of cytomegalovirus infection in bone marrow transplant recipients by prophylaxis with an intravenous hyperimmune cytomegalovirus globulin. *Birth Defects Orig. Article Ser.* **20**:327-344.
- Connor, E., and PREVENT Study Group. 1997. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. *Pediatrics* **99**:93-99.
- Cross, A. S. 1995. Intravenous immunoglobulins (IVIGs) to prevent and treat infectious diseases. *Adv. Exp. Med. Biol.* **383**:123-130.
- Cummins, L. M., K. J. Weinholt, T. J. Matthews, A. J. Langlois, C. F. Perno, R. M. Condie, and J. P. Allain. 1991. Preparation and characterization of an intravenous solution of IgG from human immunodeficiency virus-seropositive donors. *Blood* **77**:1111-1117.
- Douzinias, E. E., M. T. Pitaridis, G. Louris, I. Adrianakis, K. Katsouyanni, D. Karpaliotis, J. Economidou, D. Sfyros, and C. Roussos. 2000. Prevention of infection in multiple trauma patients by high-dose intravenous immunoglobulins. *Crit. Care Med.* **28**:8-15.
- Dowling, H. F. 1948. The acute bacterial diseases: their diagnosis and treatment, p. 26-36. The W. B. Saunders Co., Philadelphia, Pa.
- Falagas, M. E., D. R. Snyderman, R. Ruthazer, J. Griffith, B. G. Werner, R. Freeman, and R. Rohrer. 1997. Cytomegalovirus immunoglobulin (CMVIG) prophylaxis is associated with increased survival after orthotopic liver transplantation. *Clin. Transplant.* **11**:432-437.
- Fanaroff, A. A., S. B. Korones, L. L. Wright, E. C. Wright, R. L. Poland, C. B. Bauer, J. E. Tyson, J. B. Phillips III, W. Edwards, J. F. Lucey, C. S. Catz, S. Shankaran, and W. Oh. 1994. A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. *N. Engl. J. Med.* **330**:1107-1113.
- Fischer, G. W., K. W. Hunter, V. G. Hemming, and S. R. Wilson. 1983. Functional antibacterial activity of a human intravenous immunoglobulin preparation: in vitro and vivo studies. *Vox Sang.* **44**:296-299.
- Groothuis, J. R., E. A. F. Simoes, M. J. Levin, C. B. Hall, C. E. Long, W. J. Rodriguez, J. Arrobio, H. C. Meissner, D. Fulton, R. C. Welliver, D. A. Tristram, G. R. Siber, G. A. Prince, M. Van Raden, and V. G. Hemming. 1993. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. *N. Engl. J. Med.* **329**:1524-1530.
- Hemming, V. G., G. A. Prince, and G. W. Fischer. 1985. Giant cell pneumonia due to respiratory syncytial virus: a response. *Arch. Pathol. Lab. Med.* **109**:213.
- Hemming, V. G., G. A. Prince, J. R. Groothuis, and G. R. Siber. 1995. Hyperimmune globulins in prevention and treatment of respiratory syncytial virus infections. *Clin. Microbiol. Rev.* **8**:22-33.
- Hemming, V. G., G. A. Prince, R. L. Horswood, W. T. London, B. R. Murphy, E. E. Walsh, G. W. Fischer, L. E. Weisman, P. A. Baron, and R. M. Chanock. 1985. Studies of passive immunotherapy for infection of respiratory syncytial virus in the respiratory tract of a primate model. *J. Infect. Dis.* **152**:1083-1087.
- Hemming, V., R. Hall, P. Rhodes, A. Shigeoka, and H. Hill. 1976. Assessment of group B streptococcal opsonins in human and rabbit serum by neutrophil chemiluminescence. *J. Clin. Investig.* **58**:1379-1387.
- Hemming, V. G., W. Rodriguez, H. W. Kim, C. D. Brandt, R. H. Parrott, B.

- Burch, G. A. Prince, P. A. Baron, R. J. Fink, and G. Reaman. 1987. Intravenous immunoglobulin treatment of respiratory syncytial virus infections in infants and young children. *Antimicrob. Agents Chemother.* **31**:1882–1886.
23. Hill, H. R. 2000. Additional confirmation of the lack of effect of intravenous immunoglobulin in the prevention of neonatal infection. *J. Pediatr.* **137**:595–597.
24. **Impact-RSV Study Group.** 1998. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* **102**:531–537.
25. King, S. M., R. Superina, W. Andrews, D. J. Winston, S. Dunn, R. W. Busuttill, P. Colambani, and K. Pradis. 1997. Randomized comparison of ganciclovir plus intravenous immune globulin (IVIG) with IVIG alone for prevention of primary cytomegalovirus diseases in children receiving liver transplants. *Clin. Infect. Dis.* **25**:1173–1179.
26. Lambert, J. S., L. M. Mofenson, C. V. Fletcher, J. Moore, Jr., E. R. Stiehm, W. A. Meyer III, G. J. Nemo, B. J. Mathieson, G. Hirsch, C. V. Sapan, L. M. Cummins, E. Jimenez, E. O'Neil, A. Kovacs, and A. Stek. 1997. Safety and pharmacokinetics of hyperimmune anti-human immunodeficiency virus (HIV) immunoglobulin administered to HIV-infected pregnant women and their newborns. *J. Infect. Dis.* **175**:283–291.
27. Mascola, J. R., G. Stiegler, T. C. VanCott, H. Katinger, C. B. Carpenter, C. E. Hanson, H. Beary, D. Hayes, S. S. Frankel, D. L. Bix, and M. G. Lewis. 2000. Protection of macaques against vaginal transmission of a pathogenic HIV-1/SIV chimeric virus by passive infusion of neutralizing antibodies. *Nat. Med.* **6**:207–210.
28. Mease, P. J., H. D. Ochs, and R. J. Wedgwood. 1981. Successful treatment of echovirus 11 meningoencephalitis and myositis-fasciitis with intravenous immune globulin therapy in a patient with x-linked agammaglobulinemia. *N. Engl. J. Med.* **304**:1278–1281.
29. Meyers, J. D., J. Leszczynski, J. A. Zaia, N. Flournoy, B. Newton, D. R. Snyderman, G. G. Wright, M. J. Levin, and E. D. Thomas. 1983. Prevention of cytomegalovirus infection by cytomegalovirus immune globulin after marrow transplantation. *Ann. Intern. Med.* **98**:442–446.
30. Mofenson, L. M., J. Moye, J. Korelitz, J. Bethel, R. Hirschhorn, and R. Nugest. 1994. Crossover of placebo patients to intravenous immunoglobulin confirms efficacy for prophylaxis of bacterial infections and reduction of hospitalizations in human immunodeficiency virus-infected children. *Pediatr. Infect. Dis. J.* **13**:477–484.
31. Nabel, G. J., and N. J. Sullivan. 2000. Antibodies and resistance to natural HIV infection. *N. Engl. J. Med.* **343**:1263–1265.
32. Nagington, J., G. Gandy, J. Walker, and J. J. Gray. 1983. Use of normal immunoglobulin in an echovirus 11 outbreak in a special-care baby unit. *Lancet* **ii**:443–446.
33. Ohlsson, A., and J. B. Lacy. 2000. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. *Cochrane Database Syst. Rev.* **2**.
34. Ordman, C. W., C. G. Jennings, Jr., and C. A. Janeway. 1944. Chemical, clinical and immunological studies on the products of human plasma fractionation. XII. The use of concentrated normal human serum gamma globulin in the prevention and attenuation of measles. *J. Clin. Investig.* **23**:541–549.
35. Orlandini, O., A. Sass-Kortsak, and J. H. Ebbs. 1955. Serum gamma globulin levels in normal infants. *Pediatrics* **16**:575–583.
36. Ottolini, M. G., and V. G. Hemming. 1997. Prevention and treatment recommendation for respiratory syncytial virus infection: background and clinical experience 40 years after discovery. *Drugs* **54**:422–434.
37. **Physicians' Desk Reference.** 2001. Physicians' desk reference. Medical Economics Company, Montvale, N.J.
38. Prince, G. A., V. G. Hemming, R. L. Horswood, and R. M. Chanock. 1985. Immunoprophylaxis and immunotherapy of respiratory syncytial virus infection in the cotton rat. *Virus Res.* **3**:193–206.
39. Reimann, H. A. 1938. The pneumonias, p. 149–161. The W. B. Saunders Co., Philadelphia, Pa.
40. Rodriguez, W. J., W. C. Gruber, J. R. Groothuis, E. A. F. Simoes, A. J. Rosas, M. Lepow, A. Kramer, and V. Hemming. 1997. Respiratory syncytial virus immune globulin treatment of RSV lower respiratory tract infection in previously healthy children. *Pediatrics* **100**:937–942.
41. Rodriguez, W. J., W. C. Gruber, R. C. Welliver, J. R. Groothuis, E. A. F. Simoes, H. C. Meissner, V. G. Hemming, C. B. Hall, M. L. Lepow, A. J. Rosas, C. Robertsen, and A. A. Kramer. 1997. Respiratory syncytial virus (RSV) immune globulin intravenous therapy for RSV lower respiratory tract infection in infants and young children at high-risk for severe RSV infections. *Pediatrics* **99**:454–461.
42. Sandberg, K., K. Fasth, A. Berger, M. Eibl, K. Isacson, A. Lischka, A. Pollak, I. Tessin, and K. Thiringer. 2000. Preterm infants with low immunoglobulin levels have increased risk for neonatal sepsis but do not benefit from prophylactic immunoglobulin G. *J. Pediatr.* **137**:623–628.
43. Simon, C. E. 1913. An introduction to the study of infection and immunity including chapters on serum therapy, vaccine therapy, chemotherapy and serum diagnosis, p. 222–257. Lea and Febiger, Philadelphia, Pa.
44. Snyderman, D. R., B. G. Werner, B. H. Heinze-Lacey, W. P. Berardi, N. L. Tilney, R. L. Kirkman, E. L. Milford, S. I. Cho, H. L. Bush, Jr., A. S. Levey, T. B. Strom, C. B. Carpenter, R. H. Levey, W. E. Harmon, E. E. Zimmerman, M. F. Shapiro, T. Steinman, F. LoGerfo, B. Idelson, G. P. J. Schroter, J. J. Levin, J. McIver, J. Leszczynski, and G. Grady. 1987. Use of cytomegalovirus immune globulin to prevent cytomegalovirus disease in renal transplant recipients. *N. Engl. J. Med.* **317**:1049–1054.
45. Snyderman, D. R., B. G. Werner, N. L. Tilney, R. L. Kirkman, E. L. Milford, S. I. Cho, H. L. Bush, A. S. Levey, T. B. Strom, C. B. Carpenter, V. P. Berardi, R. H. Levey, W. E. Harmon, C. E. Zimmerman II, A. Katz, B. Heinze-Lacey, M. E. Shapiro, T. Steinman, F. LoGerfo, J. McIver, J. Leszczynski, J. Griffith, and F. F. Grady. 1991. A final analysis of the use of cytomegalovirus disease prevention in renal transplant recipients with cytomegalovirus immune globulin: comparison of randomized and open-label trials. *Transplant. Proc.* **23**:1357–1360.
46. Snyderman, D. R., M. McIver, J. Leszczynski, S. I. Cho, B. G. Werner, V. P. Berardi, F. LoGerfo, B. Heinze-Lacey, and G. F. Grady. 1984. A pilot trial of a novel cytomegalovirus globulin in renal transplant patients. *Transplantation* **38**:553–557.
47. Sorrentino, M., T. Powers, and the Palivizumab Outcomes Study Group. 2000. Effectiveness of palivizumab: evaluation of outcomes from the 1998–1999 respiratory syncytial virus season. *Pediatr. Infect. Dis. J.* **19**:1068–1071.
48. Spector, S. A., R. D. Gelber, N. McGrath, D. Wara, A. Barzilai, E. Abrams, Y. J. Bryson, W. M. Dankner, R. A. Livingston, E. M. Connor, and the **Pediatric AIDS Clinical Trials Group.** 1994. A controlled trial of intravenous immune globulin for the prevention of serious bacterial infections in children receiving zidovudine for advanced human immunodeficiency virus infection. *N. Engl. J. Med.* **331**:1181–1187.
49. Steen, J. A. 1960. Gamma globulin in preventing infections in premature infants. *Arch. Pediatr.* **77**:291–294.
50. Stiehm, E. R. 1979. Standard and special human immune serum globulins as therapeutic agents. *Pediatrics* **63**:101–109.
51. Stiehm, E. R. 1997. Human intravenous immunoglobulin in primary and secondary antibody deficiencies. *Pediatr. Infect. Dis. J.* **16**:696–707.
52. Stiehm, E. R., J. S. Lambert, L. M. Mofenson, J. Bethel, J. Whitehouse, R. Nugent, J. Moye, Jr., M. F. Fowler, B. J. Mathieson, P. Reichelderfer, G. J. Nemo, J. Korelitz, W. A. Meyer III, C. V. Sapan, E. Jimenez, J. Gandia, G. Scott, M. J. O'Sullivan, A. Kovacs, A. Stek, W. T. Shearer, and H. Hammill. 1999. Efficacy of zidovudine and human immunodeficiency virus (HIV) hyperimmune immunoglobulin for reducing perinatal HIV transmission from HIV-infected women with advanced disease: results of pediatric AIDS clinical trials group protocol 185. *J. Infect. Dis.* **179**:567–575.
53. Stokes, J., Jr., E. P. Maris, and S. S. Gellis. 1944. Chemical, clinical and immunological studies on the products of human plasma fractionation. XI. The use of concentrated normal human serum gamma globulin (human immune serum globulin) in the prophylaxis and treatment of measles. *J. Clin. Investig.* **23**:531–540.
54. Weisman, L. E., B. F. Anthony, V. G. Hemming, and G. W. Fischer. 1993. Comparison of group B streptococcal hyperimmune globulin and standard intravenously administered immune globulin in neonates. *J. Pediatr.* **122**:929–937.
55. Weisman, L. E., B. J. Stoll, T. J. Kueser, T. T. Rubio, C. G. Frank, H. S. Heimann, K. N. S. Subramanian, C. T. Hankens, B. F. Anthony, D. F. Cruess, V. G. Hemming, and G. W. Fischer. 1992. Intravenous immune globulin therapy for early-onset sepsis in premature neonates. *J. Pediatr.* **121**:434–443.
56. Werden, K. 1999. Supplemental immune globulins in sepsis. *Clin. Chem. Lab. Med.* **37**:341–349.